REMARKS

Amendments to Specification and Claims

Applicants have amended their specification to include portions from the original parent application Serial No. 08/713,834. These amendments are proper because the specification of the present application specifically incorporates the entire original parent application.

Original parent application Serial No. 08/713,834 is now U.S. Patent No. 6,028,064 ("the '064 patent"). The present amendments to the specification are from the original parent application as shown at the following locations in the issued U.S. Patent No. 6,028,064. The amendment at page 18, line 21 of this application is based on '064 patent, col. 9, line 67 and col.10, lines 1-15 & 59-65. The amendment at page 19, line 11 of this application is based on '064 patent, col. 7, lines 41-42. The amendment at page 20, line 4 of this application is based on '064 patent, col. 6, lines 6-31 & col.11, lines 29-67 and col.12, lines 1-6 & 32-45. The amendment at page 20, line 13 of this application is based on '064 patent, col. 4 lines 5-6. The amendment at page 20, line 20 of this application is based on '064 patent, col. 7, lines 38-41. The amendment at page 20, line 24, of this application is based on '064 patent, col.10, lines 66-67 and col. 11, lines 1-3 & 17-23.

Distinguishing the Need reference

The rejection based on the Need reference was based on Need's study to determine if certain compounds alone or in combination improved bone density. The combination of progestin plus Vitamin D was used with calcium. However, the study did not show any benefit to using the progestin/Vitamin D combination with calcium over using only one of those compounds with calcium. Nevertheless, Need did disclose the particular combination from his test, and that combination is 102 prior art.

Consequently, applicant discussed with the Examiner the idea of drafting new independent claims that distinguish over the Need reference. As discussed at the interview, those amendments should distinguish over Need, and also avoid any 103 rejection because one skilled in the art would not be motivated to combine progestin with Vitamin D for the purposes of Need. Indeed, Need's results would discourage further use of the combination. In contrast, applicants discovered an unanticipated benefit of combining progestin and Vitamin D compounds, namely prevention of ovarian cancer.

The new claims distinguish over Need for the reasons discussed at the interview. Specifically, looking at each independent claim:

- Need does discloses daily administration of both the progestin product and the Vitamin D product with no breaks in administration of those compounds. Need does not disclose daily sequential dosages where progestin is not provided on some days. Independent claim 75 requires a product adapted for such days without progestin.

- Need discloses only calcitriol. Independent claims 91 and 125 are limited to Vitamin D products other than calcitriol.

- Need has no disclosure of any gonane progestin (Need only discloses one progestin). Independent claim 112 is limited to only gonane progestins.

- Need discloses daily administration of both the progestin product and the Vitamin D product. Need does not disclose daily sequential dosages where Vitamin D is not provided for on some days. Independent claim 134 requires a product adapted for such days without progestin.

Lack of Motivation Elsewhere to Combine Vitamin D and Progestins

As discussed above, Need provides no motivation for combining progestin and Vitamin

D. Applicants provide the following background on the separate use of Vitamin D and progestin

in connection with malignant breast cells (not prevention). No motivation existed to combine Vitamin D with progestin for treatment of breast cancer cells.

1. At the time of the invention here in 1996-97, progestins were known in the art for the treatment of malignant breast cells. Progestins had been used clinically for several years for this purpose. However, by 1996-97, it was known that tamoxifen was the preferred first line treatment over progestins and other compounds. Muss, et al., *Annals of Oncology* 3:S15-S20 (1992); Muss, et al., Journal of Clinical Oncology, Vol. 12, No. 8, 1630-1638 (1994). The reason was that tamoxifen had an efficacy equivalent to progestins, but had far fewer side effects than progestins. *Id.*

It is important to note that the progestin dosage required for treatment of women with breast cancer was extremely high as compared to oral contraceptive preparations and HRT products. The standard dosage of progestin for treatment of breast cancer was ***300 milligrams to 1 gram*** of medroxyprogesterone acetate, or ***160 mg*** of megestrol acetate. Muss, et al., *Annals of Oncology* 3:S15-S20 (1992). Oral contraceptives and HRT products use only a few milligrams or less of comparable progestin equivalent..

2. At the time of the invention here in 1996-97, Vitamin D had been reported as showing some efficacy *in vitro* on malignant breast cancer cells and in vivo in animal models of breast cancer . However, Vitamin D had been used very little clinically for the treatment of women with breast cancer. In 1991, a study showed the use of Vitamin D topically on advanced breast tumors. Bower, et al., *Lancet*, Vol. 337, 701-702 (1991). However, hypercalcemia was reported. In 1998, there was a report of use of a Vitamin D analogue in a phase I clinical trial in individuals with breast or colon cancer. Gulliford, British Journal of Cancer, 78(1), 6-13 (1998).

However, the authors reported acceptable toxicity, but noted that they "failed to observe any anti-tumor effects in our patients." (*Id.* at 12).

3. At the time of the invention here in 1996-97, there was no motivation to combine Vitamin D with progestin for treatment of malignant breast cells. Vitamin D compounds were still being studying for their own efficacy. Progestin itself was not a first line treatment. There was simply no motivation to combine these two compounds. There was not even a suggestion that combining the two would have any additive effect on the treatment of breast cancer.

4. In the art of treating breast cancer, physicians use sequent treatment with different drugs, and the published evidence from clinical trials suggested that combinations of hormonal agents, or hormonal agents with chemotherapeutic agents were not more effective than using the agents singly. Locker, Cancer Treatment Reviews 23: 221-240 (1998); Vogel, Seminars in Oncology, Vol. 23, No. 4, Supp. 9, 2-9 (1996); Gill, et al., Annals of Oncology 4:741-744(1993); Lundgren, Acta Oncologica, Vol. 31, No. 7, 709-722 (1992) . Therefore, by using hormonal agents singly, physicians would achieve optimal efficacy, while minimizing side effects associated with administering more than one agent. This was particularly relevant for progestins, which were given in high dosages and associated with significant side effects. Locker, Cancer Treatment Reviews 23: 221-240 (1998); Gill, et al., Annals of Oncology 4:741-744(1993); Lundgren, Acta Oncologica, Vol. 31, No. 7, 709-722 (1992) The standard first line hormonal treatment was tamoxifen, with progestins or other hormonal agents considered as second line if tamoxifen failed.

Physicians in this art generally adhere with the sequential approach of a first line treatment of one drug and then a second line treatment with another. However, there was no

motivation in the art to combine Vitamin D with the less favored progestin for the treatment of breast cancer cells. In contrast, applicants discovered an unanticipated benefit of combining progestin and Vitamin D compounds, namely prevention of ovarian cancer.

Conclusion

Applicants respectfully seek allowance of the new claims.

Respectfully submitted,

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